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EXAMINER
PAPPU, SITA S

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1636	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/724,797	Applicant(s) THORSON, JON S.	
	Examiner Sita Pappu	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,57,58,88-101,142-146,148 and 149* is/are pending in the application.

4a) Of the above claim(s) *100,101,142-144 and 149* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,57,58,88-99,145,146 and 148* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This Office Action is a supplemental action to the Office Action mailed on 07/18/2002 (paper #12). This Office Action supersedes and replaces the previous Office Action (Paper #12) and contains the complete set of rejections being advanced against the pending claims.

Claims 1-9, 57, 58, 88-101, 142-146, 148 and 149 are pending in the instant application. This Office Action is in response to the communication filed by the Applicant on 06/06/2002 (paper #11).

Election/Restrictions

Applicant's election, with traverse, of the isolated nucleic acid molecule of SEQ ID NO:35 (Group 18, claims 1-9, 57, 58, 88-99, 145, 146, 148) encoding the amino acid sequence of SEQ ID NO:36 of calS gene, is acknowledged. Applicant traversed on the grounds that all the 48 genes included in the application are part of the "calicheamicin gene cluster" and that it would not be unduly burdensome for the examiner to search all the sequences. Applicant further quotes MPEP Section 803.04 regarding the examination of more than one sequence in a single application. In response, it is noted that "one sequence" is included within the figure of "upto ten sequences" allowed, as per MPEP 803.04. Further, it is a tremendous burden on the office's search engines and resources to search more than one sequence in a single application.

In addition, as mentioned in the restriction requirement, each of the structurally different sequences is deemed to normally constitute an independent and distinct invention within the meaning of 35 U.S.C. 121. Accordingly, only one (1) independent

and distinct nucleotide/polypeptide sequence will be examined in a single application without restriction. Therefore, the original restriction requirement is still deemed proper and is made FINAL.

Accordingly, claims 1-9, 57, 58, 88-99, 145, 146, 148 will be examined only to the extent they encompass the elected invention of an isolated nucleic acid molecule of SEQ ID NO:35 encoding the amino acid sequence of SEQ ID NO:36 of calS gene.

Claims 100, 101, 142-144, 149 are withdrawn from consideration as being directed to non-elected subject matter.

Priority

Applicant's claim of priority to the non-provisional application 09/457,045 (filed 12/07/1999, now abandoned) and provisional application 60/111,325 (filed 12/07/1998) is acknowledged.

Drawings

Draftsperson objected to the drawings. See attached PTO-948. Applicant is required to submit the drawing corrections within the time period set in this Office Action. See 37 C.F.R. 1.85(a). Failure to take corrective action within the set time period will result in ABANDONMENT OF THE APPLICATION.

Specification

The disclosure is objected to because of the following informalities: The specification refers to genes "encoding for" calicheamicin biosynthesis throughout the specification including the title. The correct usage which is either "encoding" or "coding

for" is suggested and the entire specification should be reviewed and an amendment is required with the proper usage.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-9, 57, 58, 88-99, 145, 146, 148 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The elected invention is directed to calS gene as set forth in SEQ ID NO:35 encoding a polypeptide of SEQ ID NO:36. The specification discloses (page 36, paragraph 2), that based on sequence homology with P450-oxidases, CalS appears to be a P450-oxidase homolog which performs the oxidation of intermediate 39 to intermediate 42. In addition, the specification discloses that the calS gene or a fragment of calS was cloned into an expression vector. The specification, however, fails to disclose any assays for determining the activity of CalS gene product. Further, the specification fails to disclose a substantial utility for the calS gene product, which utility is novel, substantial and tangible, other than implicating it in the calicheamicin pathway. While calicheamicins are known to exhibit antitumor activity, the utility of calS gene product of the invention is not clear other than the calS gene being implicated in the calicheamicin pathway based on its sequence homology to P450-oxidases.

Thus, the claimed invention lacks patenatble utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 57, 58, 88-99, 145, 146, 148 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and breadth of claims:

The nature of the invention is directed to an isolated nucleic acid molecule comprising calS gene from a nonchromoprotein enediyne biosynthetic gene cluster from Micromonospora echinospora, as set forth in SEQ ID NO:35 encoding a protein of SEQ ID NO:36, which has homology to P450 oxidases, an expression vector comprising the

nucleic acid molecule, host cell transformed with the vector, and a method of expressing the protein. The claims encompass the protein encoded by the nucleic acid molecule having the activity of at least one protein from nonchromoprotein enediyne biosynthetic gene cluster, especially P450 oxidases (specification, page 36, paragraph 2) based on sequence homology with other P450-oxidases which perform the oxidation of intermediate 39 to intermediate 42 in the calicheamicin biosynthetic pathway and are very broad.

State of the art, amount of guidance in the specification and working examples:

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating tile specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:246-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith etal. (1997, Nature Biotechnology 15:1222-1223) remark that

there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Without sufficient guidance, extrapolating the function from structure alone is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

The specification discloses isolation and characterization of calC (example 2, page 43) discloses calC as capable of conferring resistance to calicheamicin (page 44, paragraph 1), expression of CalC protein in E.coli (example 3, page 45), verification of CalC's calicheamicin resistance (example 4, page 45), production of methymycin/pikromycin-calicheamicin hybrid compounds (example 5, page 46) using calH gene sequence, and a method of assaying the calicheamicin-induced DNA cleavage and its CalC mediated inhibition (example 6, page 47) using molecular break light assay.

The specification fails to disclose any teachings directed to the calS gene and/or the protein encoded by the calS gene of the instant invention other than providing the sequence, and thereby the structure of the calS gene. In view of the teachings of the prior art as discussed above, it would be unpredictable to extrapolate the function of calS gene from its structure alone and would require undue experimentation on the part of a skilled artisan to use the invention.

Skill level of the artisan, amount of experimentation necessary and predictability of the art:

Although the skill of an artisan in this subject area is considered to be very high, it would require undue experimentation on the part of an artisan to make and use the invention as specified and use the invention as claimed. The specification and the working examples do not provide sufficient guidance to practice the invention as claimed. Therefore, in the absence of specific guidance and working examples, the use of the claimed polynucleotide is unpredictable. In such a situation, one skilled in the art would not know how to use the invention as claimed, without undue experimentation. In view of the limited guidance in the specification, and limited working examples, and the unpredictability of the art, one skilled in the art would be required to engage in undue experimentation, in order to use the invention.

Due to the large quantity of experimentation necessary to generate the infinite number of derivatives required and possibly screen same for establishing the activity of calS gene, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working

examples directed to calS gene, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the correlation of the protein structure with function, and the breadth of the claims, undue experimentation would be required of a skilled artisan to make and/or use the claimed invention over any scope.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkor, 19UGPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" Vas-Cath Inc. v. Mahurkar 19UGPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar 19UGPQ2d at 1116.

While the specification provides adequate written description for the claimed invention (methods and products) only with regard to the SeqID NO: 35 and the polypeptide encoded comprising the amino acid sequence set forth in SEQ ID NO:36, the specification fails to describe the other species within the genus of "nucleic acid molecules capable of hybridizing with a nucleic acid molecule from Micromonospora echinospora spp. calichensis". The specification fails to describe all the sequences

encompassed by the said genus by their complete structure and other identifying characteristics, with particularity to indicate that applicants had possession of the claimed invention. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc. 45 USpQ2d 1641, 1646 (1995). In the instant case, the claimed embodiments of any and all regulatory sequences other than those of SEQ ID NO:35 encoding a polypeptide of SEQ ID NO:36, lack a written description. The specification fails to describe what other elements fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed sequences isolated from other species, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Lfd, 18 USPQ2d 1016 (Fed. Cir. 1991).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. However, in the instant case, two specific nucleotide sequence species (SEQ ID NO:35 and the corresponding amino acid sequence SEQ ID NO:36) are described. However, the claim encompasses all sequences that can

hybridize with a DNA comprising the sequence set forth in SEQ ID NO:35 and these sequences have not been described in sufficient detail in the specification to satisfy the written description requirement. It is not at all clear that every sequence that hybridizes with SEQ ID NO:35 has an activity similar to that of SEQ ID NO:35. Sequences that hybridize with SEQ ID NO:35 encompass vastly different structures. Therefore, it is not apparent that Applicant's disclosure adequately sets forth sufficient structure/function information to describe nucleic acids that have activity similar to that of SEQ ID NO:35.

Thus, the specification must describe a representative number of encompassed species by their complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, since structure and/or function cannot be predicted from sequence, no identifying characteristics are provided for the claimed genus of sequences. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a representative number of the sequences that are encompassed by the claim, at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed sequences.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 57, 58, 88-99, 145, 146, 148 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 57, 58, 88-99, 145, 146, 148 are directed to non-elected inventions and as such the metes and bounds of the claims are not clearly set forth. Applicant is required to amend the claims such that claims 1-5, 7, 8, 9, 57, 58, 88-95, 96-99, 145, 146, 148 are directed only to the elected invention of calS gene as set forth in SEQ ID NO:35 encoding an amino acid sequence of SEQ ID NO:36.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claim 6 is rejected under 35 U.S.C. 102(a) as being anticipated by Schupp et al. (1998, PCT International Publication, WO97/08323).

Schupp et al. teach a sequence from Staurosporin biosynthesis gene cluster (Sequence 4) that has stretches of homology with SEQ ID NO; 35 of the instant invention that are capable of hybridizing with SEQ ID NO: 35. In particular, sequence 4 of WO98/08323, has 17 contiguous nucleotides (1372-1388) that are homologous to nucleotides 944-960 of SEQ ID NO: 35 and can hybridize to SEQ ID NO: 35.

Thus, Schupp et al. (1998) anticipated the invention of claim 6.

Claim 6 is rejected under 35 U.S.C. 102(a) as being anticipated by Boon-Falleur et al. (1998, U.S. patent No. 5,763,165).

Boon-Falleur et al disclose a 20 nucleotide long oligonucleotide that is used as a PCR primer of MAGE-2 gene (see SEQ ID NO:3, columns 7 and 8) that has a 15 nucleotide homology with SEQ ID NO:35 of the instant invention and is capable of hybridizing with SEQ ID NO:35.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Patard et al. (1996, U.S. Patent 5,512,444).

Patard et al disclose an oligonucleotide (see SEQ ID NO:5, columns 11 and 12) that has a 15 nucleotide homology with SEQ ID NO:35 of the instant invention and is capable of hybridizing with SEQ ID NO:35.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Boon-Falleur et al. (1995, International Publication WO95/23874).

Boon-falleur et al disclose a 20 nucleotide long oligonucleotide that is used as a PCR primer corresponding to a sense sequence exon 2 of MAGE-2 gene (see claim 7, page 91) that has a 15 nucleotide homology with SEQ ID NO:35 of the instant invention and is capable of hybridizing with SEQ ID NO:35.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Weber (1992, PCT International Publication, WO91/16334).

Weber teaches a sequence from Saccaropolyspora erythraea (Figure 3) that has stretches of homology with SEQ ID NO; 35 of the instant invention that are capable of hybridizing with SEQ ID NO: 35. In particular, EryF gene of WO91/16334, has 16 contiguous nucleotides (935-950) that are homologous to nucleotides 769-784 of SEQ ID NO: 35 and can hybridize to SEQ ID NO: 35.

Thus, Weber (1992) anticipated the invention of claim 6.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by Kunst et al. (1997, Nature, vol. 390, NO. 6657, pp.249-256).

Kunst et al. teach a nucleotide sequence from the genome of Bacillus subtilis (GenBank accession number, Z99119) that is capable of hybridizing with a nucleic acid molecule from Micromonospora echinospora spp. In particular, nucleotides 90234-90257 (a stretch of 24 contiguous nucleotides) of Z99119 encode a polypeptide

fragment that is homologous to amino acids 274-281 of SEQ ID NO: 36 and thus, can hybridize to a nucleic acid molecule from Micromonospora echinospora, which in this case is CalS gene.

Thus, Kunst et al. (1997) anticipated the invention of claim 6.

Claim 6 is rejected under 35 U.S.C. 102(e) as being anticipated by Van Baren et al. (1998, U.S. patent No. 5,985,571).

Van Baren et al disclose a 20 nucleotide long oligonucleotide that is used as a PCR primer of MAGE-2 gene (see SEQ ID NO:3, columns 7 and 8) that has a 15 nucleotide homology with SEQ ID NO:35 of the instant invention and is capable of hybridizing with SEQ ID NO:35.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sita S Pappu whose telephone number is (703) 305-5039. The examiner can normally be reached on Mon-Fri (8:30 AM - 5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on (703) 305 1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308 4242 for regular communications and (703) 872 9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst. Tracey Johnson, whose telephone number is (703) 305-2982.

Anne-Marie Baker
ANNE-MARIE BAKER
PATENT EXAMINER

S. Pappu
July 26, 2002